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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,591	08/13/2001	Tomoyasu Sugiyama		7048

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Fish & Richardson
225 Franklin Street
Boston, MA 02110-2804

EXAMINER

SISSON, BRADLEY L

ART UNIT PAPER NUMBER

1634

DATE MAILED: 02/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,591	SUGIYAMA ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4,11,13 and 14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3,4,11,13 and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3, 4, 11, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter Rejection.

For convenience, claims 1, 11, 13, and 14, the only independent claims currently pending in the instant case, are reproduced below.

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I. (Currently Amended) A hybridization probe that comprises a DNA capable of specifically hybridizing to a target nucleotide sequence, and an additional nucleotide sequence comprising one or more nucleotides selected from the group consisting of labeled nucleotides, labeled nucleotide derivatives, unlabeled nucleotides, and unlabeled nucleotide derivatives, wherein the additional nucleotide sequence consisting of a first region having a sequence which is complementary to a target nucleotide sequence and a second region, following the first region, having a sequence comprising one or more nucleotides or nucleotide derivatives selected from the group consisting of labeled nucleotides, labeled nucleotide derivatives, unlabeled nucleotides and unlabeled nucleotide derivatives, wherein the second region has a sequence that:

- a) comprises at least one nucleotide or nucleotide derivative having weaker affinity of hydrogen bonding in base pairing with bases of the target nucleotide sequence when compared with that of hydrogen bonding in an a/t pair, in an a/u pair, and or in a g/c pair;
- b) comprises either or both of at least one labeled nucleotide and labeled nucleotide derivatives; and
- c) is introduced into the DNA to be labeled through nucleotide adding reaction with terminal transferase is incapable of hybridizing under stringent conditions to any nucleotide sequence of the target nucleotide sequence.

II. (Currently Amended) A kit for synthesizing a hybridization probe, the kit comprising terminal transferase and:

- i) ~~nucleotides and/or nucleotide derivatives~~
- (a) ~~having weaker affinity of hydrogen bonding in base pairing when compared with those of hydrogen bonding in an a/t pair, in an a/u pair, and in a g/c pair, and~~
- (b) ~~being introduced into a DNA comprising a nucleotide sequence complementary to the target nucleotide sequence through nucleotide adding reaction with terminal transferase;~~
- ii) ~~labeled nucleotides or nucleotide derivatives; and~~
- iii) ~~terminal transferase~~
- i) unlabeled nucleotides and/or unlabeled nucleotide derivatives
- ii) labeled nucleotides and/or labeled nucleotide derivatives
- wherein at least one nucleotide or nucleotide derivative has weaker affinity of hydrogen bonding in base pairing when compared with those of hydrogen bonding in an a/t pair, in an a/u pair, or in a g/c pair.

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13. (Currently Amended) A hybridization probe that comprises a DNA capable of specifically hybridizing to a target nucleotide sequence, and an additional nucleotide sequence comprising one or more nucleotides selected from the group consisting of labeled nucleotides, labeled nucleotide derivatives, and unlabeled nucleotide derivatives, wherein the additional nucleotide sequence comprising a first region having a sequence complementary to a target nucleotide sequence and a second region having a sequence comprising one or more nucleotides or nucleotides derivatives selected from the group consisting of labeled nucleotides, labeled nucleotide derivatives, and unlabeled nucleotide derivatives, wherein the second region has a sequence that:

- a) comprises at least one nucleotide or nucleotide derivative having weaker affinity of hydrogen bonding in base pairing with bases of the target nucleotide sequence when compared with that of hydrogen bonding in an a/t pair, in an a/u pair, and or in a g/c pair;
- b) comprises either or both of at least one labeled nucleotide and labeled nucleotide derivatives; and
- c) is introduced into the DNA to be labeled through nucleotide adding reaction with terminal transferase which is incapable of hybridizing under stringent conditions to any nucleotide sequence of the target nucleotide sequence.

14. (Currently Amended) A kit for synthesizing a hybridization probe, the kit comprising terminal transferase and the following nucleotides and/or nucleotide derivatives:

- i) nucleotide derivatives
 - (a) having weaker affinity of hydrogen bonding in base pairing when compared with those of hydrogen bonding in an a/t pair, in an a/u pair, and in a g/c pair; and
 - (b) being introduced into a DNA comprising a nucleotide sequence complementary to the target nucleotide sequence through nucleotide adding reaction with terminal transferase;
- ii) labeled nucleotides or nucleotide derivatives; and
- iii) terminal transferase
- i) unlabeled nucleotide derivatives
- ii) labeled nucleotides and/or labeled nucleotide derivatives
wherein at least one nucleotide or nucleotide derivative has hydrogen bonding base pairing affinity that is weaker than that of an a/t pair, an a/u pair, or a g/c pair.

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3. For purposes of examination, the probe of claims 1, 3, 4, and 13 has been interpreted as encompassing both DNA and RNA sequences. A review of the disclosure fails to find support for such breadth of scope. Rather, the specification teaches explicitly, and was reflected in the original claims, that the probe is DNA. Accordingly, the amendment to claims 1 and 11 has resulted in the introduction of new matter into the claims. Claims 3 and 4, which depend from claim 1, fail to overcome this issue and are similarly rejected.

4. The specification has not been found to contain such a full, clear, and concise written description of the claimed probes and kits as to reasonably suggest that applicant was in possession of same at the time of filing. As presently worded, the claimed inventions are considered to encompass probes that can be used to detect virtually any nucleotide sequence, in any life form, including, but not limited to the detection of any disease or predisposition to any disease, state or condition known as well as not yet known. A review of the specification fails to find where any probes have been described such that one of skill in the art would be able to identify and differentiate probes encompassed by the claims from those that are not so encompassed.

5. Page 8, last paragraph, bridging to page 9 of the specification states in pertinent part:

In order to achieve such conditions, it is necessary to increase the proportion of the above-mentioned nucleotides (or nucleotide derivatives) exhibiting weak base pairing in the sequence to be added for labeling. Since the minimum proportion depends on the type of nucleotide, the composition of co-existing nucleotides, and the total length, it is difficult to show the typical range. However, those skilled in the art can empirically determine the proportion based on the disclosure of the present invention. (Emphasis added)

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Rather than provide the public with a full, clear, and concise description of the claimed probes, including the number and type of nucleotides or nucleotide derivatives that would exhibit the requisite weak base pairing, applicant is unfairly shifting the burden of providing the requisite written description to that of the public and in so doing is relying upon obviousness.

Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

Accordingly, and in the absence of convincing evidence to the contrary, the specification fails to provide an adequate written description of the probes of claims 1, 3, 4, and 13.

6. Claims 11 and 14 are drawn to kits that are to be used in making the claimed probes. As presented above, the specification fails to provide an adequate written description of just what the nucleotide sequence of the probes are. Accordingly, the specification fails to provide an adequate written description of how the claimed kit components are to be used such that the alleged novel and non-obvious probes can be realized.

7. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1, 3, 4, 11, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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9. Claims 1, 3, 4, 11, 13, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The term "stringent conditions" in claims 1 and 13 is a relative term, which renders the claims indefinite. The term "stringent conditions" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 3 and 4, which depend from claim 1, fail to overcome this issue and are similarly rejected.

11. Claims 1 and 13 are confusing as to just what the "second region" is to have in terms of "a sequence" as a review of both claims finds two clauses directed to defining said second region, and in so doing create a conflict. In particular, the first clause stipulates that the second region has a sequence that comprises:

One or more nucleotides or nucleotide derivatives selected from the group consisting of labeled nucleotides, labeled nucleotide derivatives, unlabeled nucleotides and unlabeled nucleotide derivatives.

In contrast, the same claims also define the second region as having a sequence that:

- a) comprises at least one nucleotide or nucleotide derivative having weaker affinity of hydrogen bonding in base pairing with bases of the target nucleotide sequence when compared with that of hydrogen bonding in an a/t pair, in an a/u pair, or in a g/c pair;
- b) comprises either or both of at least one labeled nucleotide and labeled nucleotide derivatives; and
- c) is incapable of hybridizing under stringent conditions to any nucleotide sequence of the target nucleotide sequence.

12. It is noted that in the first clause, the alternative (or) is used to define that which is present, and in so doing, no labeled nucleotide or labeled nucleotide derivative need be present,

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yet in the second instance, there must be a labeled nucleotide or labeled nucleotide derivative present.

13. Additionally, the number of such residues is not in agreement in the second clause; note the use of “one” as in “one labeled nucleotide” in combination with “derivatives.”

14. As a result of this internal conflict in claim language, it is not readily apparent just what the probe must comprise. Claims 3 and 4, which depend from claim 1, fail to overcome this issue and are similarly rejected.

15. Claims 11 and 14 are confusing where there is no modifier (e.g., “or” or “and”) between limitations i) and ii). As a result, it is not clear if i) must occur with ii) or whether either could occur independent of the other.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,388,063 B1 (Plowman et al.) in view of Mills et al.

20. Plowman et al., columns 15 and 23 teaches of the variety of formants that kits may take, and that they may include any reagents that are used in any of the disclosed methods, which include nucleic-based assays. Plowman et al., teach specifically of using nucleotides and nucleotide derivatives in the development of primers/primers. Column 34 teaches explicitly of using a terminal transferase.

21. Plowman et al., do not teach using nucleotide or nucleotide derivatives that “has hydrogen base pairing affinity that is weaker than that of an a/t pair, an a/u pair, or a g/c pair.”

22. Mills et al., teach explicitly of using probes that comprise nucleotide derivatives (inosine-substituted). Such nucleotide derivatives are recognized as having “hydrogen base pairing affinity that is weaker than that of an a/t pair, an a/u pair, or a g/c pair.” Mills et al., provides motivation for using such nucleotide derivatives at page 2232 wherein they are disclosed as greatly reducing, if not eliminating certain secondary structures.

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23. In view of the combined teachings of the prior art of record, it would have been obvious to one of ordinary skill in the art to have combined nucleotides, nucleotide derivatives, be they labeled and/or unlabeled into a kit which also comprises a terminal transferase as such would have allowed for the ready development and use of probes for the detection of genetic disorders. In view of the detailed guidance provided in the prior art, the ordinary artisan would have had a most reasonable expectation of success. Therefore, and in the absence of convincing evidence to the contrary, claims 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,388,063 B1 (Plowman et al.) in view of Mills et al.

Conclusion

24. Rejections and/or objections that appeared in the prior Office action and not repeated hereinabove have been withdrawn.

25. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

26. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751.

The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

28. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
02 February 2005